## REMARKS

Claims 48-66 and 77-96 are pending in the present application and at issue.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

### I. The Rejection of Claims 48-50, 56-59, 65, 66, 77-79, 85-89, 95 and 96 under 35 U.S.C. 102 or 103

The Office maintained the rejection of claims 48-50, 56-59, 65, 66, 77-79, 85-89, 95 and 96 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ladner et al. (U.S. Patent No. 5,223,409). Specifically, the Office stated:

> Applicant suggests that the disclosure of Ladner et al. of modification of the amino acid sequence of a polypeptide, the medicinally active enzyme streptokinase, that is "antigenic to an undesirable extent' to produce a variant polypeptide with reduced allergenicity is deficient because Ladner et al. (1) map antigenic epitopes generally during their screening procedure, rather than specifically, a priori, (2) do not explicitly state that a resulting, epitope-reduced streptokinase be functional, and, (3) do not require that the IgE response to the altered, epitope-reduced, enzyme be reduced to render it less allergic in animals. In each instance, Applicant argues limitations absent from the claims.

This rejection is respectfully traversed.

Applicants also respectfully disagree that they are arguing limitations absent from the claims. For example, all of the claims require that the variant be functional.

#### A. Ladner et al. Do Not Disclose or Suggest Mapping An Epitope, as Required By Applicants' Methods

Ladner et al. disclose a method of producing phage libraries of variants by controlled random mutagenesis ("variegation") and then selecting phages bearing those variants that do not bind to a target. The Ladner et al. method involves controlling the variegation to target amino acid residues located on the surface of streptokinase and raising an antibody against streptokinase for attachment to a column. The variants are selected by being placed in the antibody column and phages bearing those variants that do not bind to the column are collected and cultured.

However, Ladner et al. never map an epitope, i.e., Ladner et al. never identify the amino acids that form an epitope. Instead, Ladner et al. select variants that do not bind to the antibody column or which bind weakly when eluted in a salt gradient. Although some of these variants may

have a mutation of an amino acid that forms an epitope, Ladner et al. do not disclose or suggest which mutations belong to an epitope or which mutations belong to the same epitope. For example, a variant selected by the method of Ladner et al. might contain five amino acid substitutions, three of which are part of epitopes, and two of which are due to the randomness of the variegated library design. Ladner et al. do not suggest any method of determining which of the five mutations are mutations of an epitope and which are not. Furthermore, Ladner et al. do not suggest any method of determining whether the three mutations that are mutations of an epitope are mutations of the same or different epitope.

Moreover, Ladner et al. state that, "Destroying binding frequently requires only that a single amino acid in the binding interface be changed." This indicates that Ladner et al. are not interested in mapping any epitope.

For the foregoing reasons, Ladner et al. do not map one or more epitopes of a reference protein.

At page 5, lines 17, 18 of the Office Action, the Office states that Ladner et al. "disclose many examples of practicing each step of the method taught in section 'V.R.'" This is respectfully traversed.

As mentioned in the previous response, the general objective of and all the working examples of Ladner et al. are directed to selecting variants that have increased binding to a target. Only in section 'V.R.' does the Ladner et al. reference (from column 102, line 44 – column 103, line 30) aim to select variants that do not bind to the target or bind less strongly to the target. This section is not supported by any working examples. As indicated in the previous response, the difference between selecting for increased binding and decreased binding is fundamental in nature because selecting for decreased binding will inherently be a selection for all the members of the phage library, which contain misfolded, inactivated, misprocessed, truncated, or otherwise dysfunctional variants of the target protein. Thus, the statement in Ladner et al. at column 103, lines 5-8, that "such mutants are tested to verify that the pharmacologically interesting properties have not been altered to an unacceptable degree by the mutations' would be understood by one of ordinary skill in the art to require an enormous testing program in order to identify functional variants. Thus, Ladner et al. do not disclose or suggest a method for mapping epitopes of a protein with a reasonable likelihood of success.

**B. Ladner et al. Do Not Disclose or Suggest Raising Antibodies Against the Reference protein and Variants Thereof, as Required by the Method of Claim 77**

In the Ladner et al. method, an antibody is raised against the reference protein and not against the reference protein and a variant thereof, as recited in claim 77. Thus, Ladner et al. do not teach or suggest the methods of claims 77-86.

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. 102 and 103. Applicants respectfully request reconsideration and withdrawal of the rejections.

**II. The Rejection of Claims 51-53, 60-62, 80-82, and 90-92 under 35 U.S.C. 103**

The Office maintained the rejection of claims 51-53, 60-62, 80-82 and 90-92 under 35 U.S.C. 103(a) as being obvious over Ladner et al. in view of either Zachariae et al. (Allergy, Vol. 36, pp. 513-516 (1981)) or Arlian et al. (Int. Arch. Allergy Appl. Immunol., Vol. 91, pp. 278-284 (1990)). This rejection is respectfully traversed.

As provided in Section I, Ladner et al. do not teach or suggest the methods of the present invention. Applicants submit that Zachariae et al. and Arlian et al. fail to cure the deficiencies of Ladner et al.

Zachariae et al. disclose that exposure to detergent enzymes like Esperase® will cause IgE-mediated sensitization in persons.

Arlian et al. disclose that Alcalase and Savinase cause respiratory allergy. However, Arlian et al. is also silent with respect to teaching the method, as claimed herein.

However, neither Zachariae et al. nor Arlian et al. teach or suggest methods for producing a DNA molecule encoding a variant of a reference protein, comprising mapping one or more epitopes of a reference protein and forming a DNA molecule encoding a variant, which has an altered amino acid sequence of one or more epitopes of the reference protein, wherein the variant evokes a lower immunogenic response in an animal than the reference protein.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 103(a). Applicants respectfully request reconsideration and withdrawal of the rejection.

**III. Conclusion**

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to

contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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